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Unified Synthesis of Eudesmanolides, Combining Biomimetic Strategies with Homogeneous Catalysis and Free-Radical Chemistry

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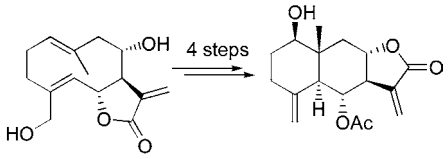
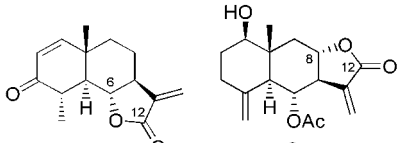
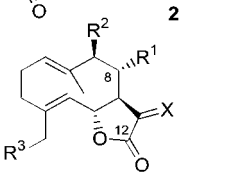
ABSTRACT



A general procedure for the synthesis of both 12,6- and 12,8-eudesmanolides has been developed. The key step is the titanocene-catalyzed radical cyclization of accessible epoxygermacrolides. The novel reagent 2,4,6-trimethyl-1-trimethylsilylpyridinium chloride, both compatible with oxiranes and capable of regenerating Cp_2TiCl_2 from $Cp_2Ti(Cl)H$ and $Cp_2Ti(Cl)OAc$, played an important role in the catalytic cycle leading to exocyclic alkenes.

General methods for the synthesis of large families of natural products might be more productive than specific procedures restricted to the preparation of just one or a few compounds. Eudesmanolides constitute one of the main groups of natural sesquiterpenoids, with more than 500 members described to date.[1] These compounds have been classified into two subfamilies: 12,6-eudesmanolides such as (+)-tuberiferine (**1**) and 12,8-eudesmanolides such as (+)-β-cyclopyrethrosin (**2**).[1] Their pharmacological properties include antifungal, antiinflammatory, and antitumoral activities and the capacity to inhibit human topoisomerase II, among others.[2] Nevertheless, many of them are scarce in nature and so chemists have developed several synthetic processes.[3] The methods described to date, however, are specific for a few products, require numerous steps, and generally provide low overall yields. A general procedure for the effective synthesis of eudesmanolides therefore seemed desirable.





3, R^1 = H, R^2 = H, R^3 = H, X = αCH_3, βH
4, R^1 = H, R^2 = H, R^3 = H, X = CH_2
5, R^1 = H, R^2 = OH, R^3 = OH, X = CH_2
6, R^1 = OH, R^2 = H, R^3 = OH, X = CH_2

As germacrolides are the biogenetic precursors of eudesmanolides,[1a] and some of them such as (+)-dihydro-

(1) (a) Fischer, N. H.; Olivier, E. J.; Fischer, H. D. *Prog. Chem. Org. Nat. Prod.* **1979**, *38*, 134−165. (b) Connolly, J. D.; Hill, R. A. *Dictionary of Terpenoids*; Chapman and Hall, London, 1991; Vol. 1, pp 340−371. (c) Fraga, B. M. *Nat. Prod. Rep.* **2002**, *19*, 650−672 and previous issues in this series.

(2) (a) Hehner, S. P.; Heinrich, M.; Bork, P. M.; Vogt, M.; Ratter, F.; Lehmann, V.; Schulze-Osthoff, K.; Dröge, W.; Schmitz, M. L. *J. Biol. Chem.* **1998**, *273*, 1288−1297. (b) Dirsch, V. M.; Stuppner, H.; Ellmerer-Müller, E. P.; Vollmar, A. M. *Bioorg. Med. Chem.* **2000**, *8*, 2747−2753. (c) Skaltsa, H.; Lazari, D.; Panagouleas, C.; Georgiadou, E.; García, B.; Sokovic, M. *Phytochemistry* **2000**, *55*, 903−908

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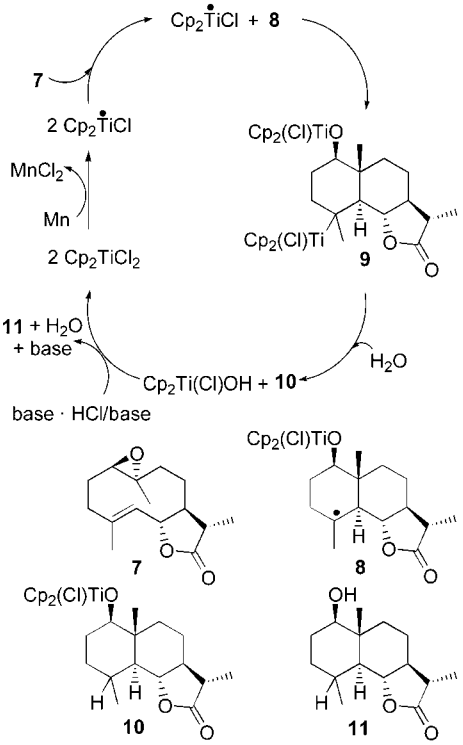
costunolide (**3**), (+)-costunolide (**4**), (+)-stenophyllolide (**5**), and (+)-salonitenolide (**6**) are accessible in (multi)gram quantities,[4] we planned to employ these raw materials in a biomimetic synthesis of eudesmanolides. The results obtained using carbocationic chemistry, however, were quite discouraging because of product mixtures, and only poor yields were obtained;[4b,5] therefore, we assayed free-radical chemistry.[6] Thus, we achieved the synthesis of some eudesmanolides applying the stoichiometric version of the method reported by RajanBabu and Nugent,[7] but we required considerable amounts of Cp_2TiCl_2 to obtain acceptable yields.[4b] These observations prompted us to develop a novel procedure for the synthesis of eudesmanolides catalyzed by titanocene.

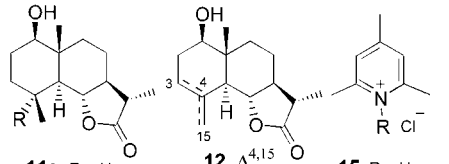
Our initial hypothesis was based on the assumption that a single electron transfer between $Cp_2Ti^{III}Cl$ generated in situ[8] and an epoxygermacrolide such as **7** should promote a rearrangement process giving tertiary radical **8** (Scheme 1).

Scheme 1. Hypothetical Catalytic Cycle in Aqueous Medium; Base: 2,4,6-Collidine



Subsequent C−Ti coupling between **8** and a second $Cp_2Ti^{III}Cl$ species would lead to the alkyl−Ti^{IV} complex **9**, which, after hydrolysis, would provide **10** and $Cp_2Ti(Cl)$-OH. So far, only two types of reagents have been described to regenerate Cp_2TiCl_2 from species of oxygen-bonded titanium: chlorosilanes and protic compounds closely related with collidine hydrochloride (**15**).[9] The former are strong Lewis acids incompatible with oxiranes, while the weak acid **15** is not suitable for regenerating Cp_2TiCl_2 from acetoxytitanium derivatives. Acidic reagents, moreover, easily promote the carbocationic rearrangement of epoxygermacrolides, giving rise to undesirable byproducts and a concomitant decrease in the yield from the radical process.[4b] Fortunately, the acid-promoted rearrangement of epoxygermacrolides can be prevented by adding pyridine or related bases,[5a] and therefore we chose the combination of **15** plus collidine used by Gansäuer et al. to regenerate Cp_2TiCl_2.[9b] Finally, Cp_2TiCl_2 should be transformed back into Cp_2TiCl by the surplus of Mn in the medium, and thus the catalytic cycle would be completed. To check our hypothesis, we stirred **7**, prepared from **3**,[4b] with a substoichiometric quantity of Cp_2TiCl_2 (20 mol %), Mn dust, H_2O, **15**, and collidine for 7 h at 25 °C. In this manner, we obtained the desired eudesmanolide **11** (only the (4*S*)-epimer **11a**[4b]) accompanied by a small amount of **12**[10] but no detectable carbocationic rearrangement products (e.g., **13** and **14**) (Table 1, entry 1).

Table 1. Relative Proportions[a] (%) of Compounds Obtained via Cyclization of **7**[b]



entry	Cp_2TiCl_2[c]	additives (equiv)	**11a**	**12**	**13**	**14**
1	20	H_2O (5), **15** (5), col.[d] (5)	82	18		
2	20	**15** (5), col. (5)	60	40		
3	20	Me_3SiCl (4), col. (7)	18	74	8	
4	10	H_2O (5), **15** (5), col. (5)	80	20		
5	5	H_2O (5), **15** (5), col. (5)	50	27	23	
6		H_2O (5), **15** (5), col. (5)		34	31	35

[a] Determined by ^1H NMR spectroscopy. [b] Cyclizations performed by stirring **7** with or without Cp_2TiCl_2, Mn dust (excess), and different additives in THF at 25 °C. [c] Proportions in mol %. [d] Col. = 2,4,6-collidine.

Flash chromatography provided **11a** (72% yield) supporting the concepts outlined in Scheme 1.

(3) Some selected examples: (a) Schultz, A. G.; Godfrey, J. D. *J. Am. Chem. Soc.* **1980**, *102*, 2414−2428. (b) Blay, G.; Cardona, L.; García, B.; Pedro, J. R. *J. Org. Chem.* **1993**, *58*, 7204−7208. (c) Watson, F. C.; Kilburn, J. D. *Tetrahedron Lett.* **2000**, *41*, 10341−10345.

(4) Compounds **3** and **4** can be obtained from commercially available Costus Resinoid, while **5** and **6** can be isolated from *Centaurea calcitrapa* and *C. malacitana* by simply immersing these weeds in Cl_3CH; see: (a) Barrero, A. F.; Oltra, J. E.; Barragán, A.; Álvarez, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 4107−4113. (b) Barrero, A. F.; Oltra, J. E.; Cuerva, J. M.; Rosales, A. *J. Org. Chem.* **2002**, *67*, 2566−2571. (c) Barrero, A. F.; Oltra, J. E.; Álvarez, M.; Rosales, A. *J. Org. Chem.* **2002**, *67*, 5461−5469.

(5) (a) Barrero, A. F.; Oltra, J. E.; Morales, V.; Álvarez, M. *J. Nat. Prod.* **1997**, *60*, 1034−1035. (b) Barrero, A. F.; Oltra, J. E.; Álvarez, M. *Tetrahedron Lett.* **1998**, *39*, 1401−1404.

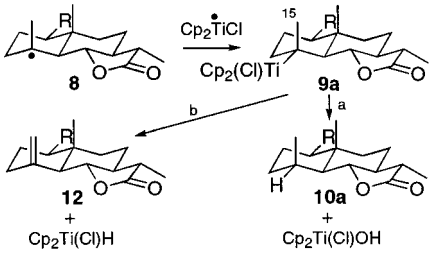
(6) For a recent overview on contemporary free-radical chemistry, see: *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; VCH: Weinheim, Germany, 2001; Vols. 1 and 2.

(7) RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986−997.

(8) Cp_2TiCl can be generated in situ by stirring commercially available Cp_2TiCl_2 and Mn dust; see: (a) Sekutowski, D.; Jungst, R.; Stucky, G. D. *Inorg. Chem.* **1978**, *17*, 1848−1855. (b) Enemaerke, R. J.; Hjollund, G. H.; Daasbjerg, K.; Skrydstrup, T. *Compt. Rend. Acad. Sc. II* **2001**, *4*, 435−438.

The stereoselectivity observed might well be ascribed to equatorial attack by the bulky Cp_2TiCl species against **8** to give **9a** (Scheme 2). The intermediate **9a** should then undergo

Scheme 2. Proposed Mechanism for the Formation of **10a** and **12**[a]



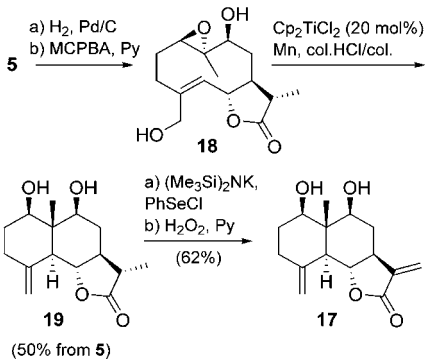
[a] R = OTi(Cl)Cp_2; (a) hydrolysis, (b) β-hydrogen elimination.

hydrolysis to produce **10a**, which would in turn give **11a** after acidic quenching. The alkyl−Ti^{IV} complex **9a** could also account for the minor quantity of alkene **12** derived from a relatively slow β-hydrogen elimination or any other process generating $Cp_2Ti(Cl)H$.[11] This possibility led us to take advantage of this process to synthesize eudesmanolides with an exocyclic $\Delta^{4,15}$ double bond.[12] Treatment of **7** in the absence of water, however, gave a mixture containing a relatively high proportion (60%) of the reduction product **11a** (Table 1, entry 2), presumably due to the protonolysis of the C−Ti bond of **9a** by the hydrochloride **15** employed.[13] Therefore, we assayed a novel reagent, the aprotic derivative **16** (prepared in situ by mixing collidine and Me_3SiCl), to regenerate Cp_2TiCl_2 and prevent protonolysis.

Treatment of **7** under these new conditions (entry 3) gave a substantially increased proportion of the exocyclic alkene **12** (74%) and a significant decrease (down to 18%) in the hydrolysis product **11a** (which might derive from adventitious water). The regeneration of the catalyst might be rationalized by reaction between **16** and the β-elimination product $Cp_2Ti(Cl)H$, giving Cp_2TiCl_2 together with collidine and gaseous Me_3SiH, but in the absence of experimental evidence, alternative explanations cannot be discarded. In any case, the minor amount of **13**[14] obtained (8%) indicated that the participation of a carbocationic process was considerably restricted.[15] Thus, **16** becomes the first example of a new type of reagent that is both compatible with epoxides and capable of regenerating Cp_2TiCl_2 from $Cp_2Ti(Cl)H$ and (as we will see later) acetoxy-titanium derivatives. The above results reveal the versatile nature of the catalytic procedure, which can be controlled to afford either reduction products or alkenes by adding or excluding water and using the additives **15** or **16**, respectively. We subsequently diminished the catalyst proportions to determine the minimum required to guarantee the radical nature of the process. With 0.05 equiv (entry 5), **11a** was still the main product, while in the complete absence of Cp_2TiCl_2 (entry 6), the mixture containing diol **14**[14] obtained was characteristic of a purely carbocationic process, confirming the crucial role played by the titanium catalyst.

To explore the synthetic usefulness of the method, we chose as targets two eudesmanolides belonging to different subfamilies: (+)-9β-hydroxyreynosin (**17**) and (+)-β-cyclopyrethrosin (**2**). 12,6-Eudesmanolide **17** and its derivative **19** were isolated from *Inula heterolepis* and *Artemisia herba-alba*, respectively, and their structures were established by spectroscopic techniques.[16] We started their synthesis with **5**, which, after selective hydrogenation and treatment with MCPBA, afforded oxirane **18** (Scheme 3). Subsequent

Scheme 3. Biomimetic Synthesis of **17** and **19**



titanocene-catalyzed cyclization of **18** gave alkene **19**. In this case, the β-elimination of the C-15 hydroxyl group was much faster than β-hydrogen elimination from **9a**, and neither anhydrous conditions nor **16** were required. Finally, the conjugated double bond was restored in a single-pot reaction applying a slight modification of Grieco's method.[17] Thus, we obtained **17** in four steps at an overall yield of 31%. The spectroscopic properties of synthetic compounds **17** and **19** were in agreement with those of the natural products.[16]

The 12,8-eudesmanolide **2** was isolated from pyrethrum flowers, and its structure was established by spectroscopic

(9) (a) Fürstner, A.; Hupperts, A. *J. Am. Chem. Soc.* **1995**, *117*, 4468−4475. (b) Gansäuer, A.; Bluhm, H.; Pierobon, M. *J. Am. Chem. Soc.* **1998**, *120*, 12849−12859. (c) Hansen, T.; Daasbjerg, K.; Skrydstrup, T. *Tetrahedron Lett.* **2000**, *41*, 8645−8649.

(10) Ogura, M.; Cordell, G. A.; Farnsworth, N. R. *Phytochemistry* **1978**, *17*, 957−961.

(11) Despite the fact that we could not isolate $Cp_2Ti(Cl)H$, previous results suggest that it might be formed from certain alkyl−Ti^{IV} complexes and possibly displays reductive properties similar to those of $Cp_2Zr(Cl)H$ (the Schwartz reagent).[4b] For a theoretical study on the reactivity of $Cp_2Ti(Cl)H$, see: Sakai, S. *J. Mol. Struct.:* THEOCHEM **2001**, *540*, 157−169.

(12) There are more than 170 natural eudesmanolides described containing a $\Delta^{4,15}$ double bond.[1]

(13) As **15** is more acidic than H_2O, the different results summarized in entries 1 and 2 of Table 1 might seem somewhat anomalous. To rationalize these results and the counterintuitive sequence given in Scheme 1, one of the referees suggested that water could act as a very good ligand for Ti that would increase the reduction potential and diminish the tendency toward β-elimination.

(14) Ando, M.; Takase, K. *Tetrahedron* **1977**, *33*, 2785−2789.

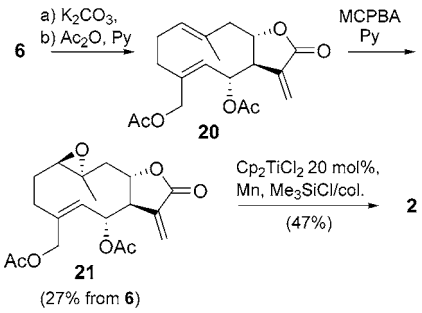
(15) Compound **13** derives from the acid-induced cyclization of **7**.[4b]

(16) (a) Bohlmann, F.; Ates, N.; Grenz, M. *Phytochemistry* **1982**, *21*, 1166−1168. (b) Ahmed, A. A.; Abou-El-Ela, M.; Jakupovic, J.; Seif-El-Din, A. A.; Sabri, N. *Phytochemistry* **1990**, *29*, 3661−3663.

(17) For the two-step original method, see: Grieco, P. A.; Nishizawa, M. *J. Org. Chem.* **1977**, *42*, 1717−1720.

methods and some chemical correlations.[18] We began its synthesis with **6**, which, after alkaline isomerization, provided the 12,8-germacrolide **20** (Scheme 4). Selective epoxidation

Scheme 4. Biomimetic Synthesis of **2**



of **20** followed by the titanocene-catalyzed cyclization of **21** gave eudesmanolide **2**, thus obtained in four steps in an overall yield of 13%. The spectroscopic data for synthetic **2**, including optical rotation, were in agreement with those of (+)-*β*-cyclopyrethrosin,[18] confirming the structure and absolute stereochemistry of the natural product.[19] In this case, we used the novel additive **16**, confirming the utility of this reagent for regenerating Cp_2TiCl_2 from $Cp_2Ti(Cl)OAc$.

The synthesis of eudesmanolides **2**, **17**, and **19** proved the utility of our method. It also occurred to us that in addition to this, the synthetics **2**, **11a**, **17**, and **19** could well be used as raw materials for the enantiospecific synthesis of many other eudesmanolides.[20] To test our idea, we set about (+)-tuberiferine (**1**), one of the most significant examples of bioactive eudesmanolides. Tuberiferine, found in *Sonchus tuberifer Svent*,[21] has been synthesized by various groups[22] and has been shown to inhibit cell growth, regulate plant development, and help control crop diseases.[22c] The most recent synthesis of **1** started from (−)-α-santonin (**22**) and was achieved in nine steps, an improvement over previous procedures.[22c] When we started its synthesis with **11a**, we obtained **1** after only six steps (see Supporting Information). Along the same line, compounds **2**, **17**, and **19** might be employed to obtain other natural eudesmanolides with practically every functionality pattern.

In summary, here we describe a novel method for the synthesis of both 12,6- and 12,8-eudesmanolides via free-radical chemistry by combining titanocene catalysis with a biomimetic strategy starting from accessible germacrolides. This procedure uses inexpensive reagents, works at room temperature under mild conditions compatible with several functional groups, and employs titanium quantities an order of magnitude lower than those required for the stoichiometric version. At the moment, we are applying this method to obtain potent antifungal eudesmanolides and more complex terpenoids.

Acknowledgment. This work was supported by the Spanish DGICYT (PB98-1365) and by a graduate fellowship from the Spanish MEC to A.R. We thank our English colleague Dr. J. Trout for his revision of our English text.

Supporting Information Available: Titanocene-catalyzed cyclization of **7** (model experimental procedure) and a scheme of the synthesis of **1** from **11a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) (a) Doskotch, R. W.; El-Feraly, F. S. *Can. J. Chem.* **1969**, *47*, 1139−1142. (b) Cardona, M. L.; Fernández, I.; B. García, J. R. Pedro, *J. Nat. Prod.* **1990**, *53*, 1042−1045.

(19) Absolute configuration of **6** is known; see: Barrero, A. F.; Oltra, J. E.; Rodríguez-García, I.; Barragán, A.; Álvarez, M. *J. Nat. Prod.* **2000**, *63*, 305−307.

(20) Reported methods for transforming α-santonin (**22**) into other terpenoids might be advantageously applied to obtain eudesmanolides from **2**, **11a**, **17**, and **19**. For a review on chemical transformations of **22**, see: Blay, G.; Cardona, L.; García, B.; Pedro, J. R. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 2000; Vol. 24, pp 53−129.

(21) Bermejo-Barrera, J.; Bretón, J. L.; Fajardo, M.; González, A. G. *Tetrahedron Lett.* **1967**, *8*, 3475−3476.

(22) (a) Yamakawa, K.; Nishitani, K.; Tominaga, T. *Tetrahedron Lett.* **1975**, *16*, 2829−2832. (b) Grieco, P. A.; Nishizawa, M. *J. Chem. Soc., Chem. Commun.* **1976**, 582−583. (c) Ando, M.; Wada, T.; Kusaka, H.; Takase, K.; Hirata, N.; Yanagi, Y. *J. Org. Chem.* **1987**, *52*, 4792−4796.